REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant RCE response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133.

Status of the Claims

Pending claims

Claims 1, 3 to 11, 25, 27 to 30, 32 to 39, 43 and 44, are pending and under consideration.

Outstanding Rejections

The rejection of claims 1, 3 to 11, 25, 27 to 30, 32 to 39, 43 and 44 under 35 U.S.C. §103, alleging these claims obvious over Morton, et al., WO 95/15338; hereinafter "Morton, WO 95/15338") in view of The Interferon Beta Multiple Sclerosis Study Group (Neurology, 1993, 43:655-661; hereinafter "the MS Study"), has been maintained for claims previously pending, and newly applied to claims 43 and 44.

Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the claim amendments

The specification sets forth an extensive description of the invention in the new and amended claims. For example, support for methods that administer IFN-β at a dose that does not produce IFN-β–induced side effects in the individual, can be found, inter alia, on page 12, lines 10 to 13, of WO 00/43033 (the publication of the priority document PCT/AU00/00032). Support for claims directed to methods that administer IFN-β at doses that would be clinically ineffective if the IFN-β was administered alone can be found, inter alia, on page 13, lines 3 to 6, of the specification. Accordingly, no new matter has been added by the instant amendments.

Issues under 35 U.S.C. §103

The rejection of claims 1, 3 to 11, 25, 27 to 30, 32 to 39, 43 and 44 under 35 U.S.C. §103, alleging these claims as obvious over Morton, et al., WO 95/15338; hereinafter "Morton,

WO 95/15338") in view of The Interferon Beta Multiple Sclerosis Study Group (Neurology, 1993, 43:655-661; hereinafter "the MS Study"), has been maintained for claims previously pending, and newly applied to claims 43 and 44 (see e.g., paragraph 4, pages 2 to 5, of the Final OA).

Applicants respectfully traverse and expressly incorporate their previous responses herein, including the submitted expert declarations by Dr. Johnson (see response of October 27, 2005) and Dr. Pamela McCombe (see response of October, 2006).

In brief, Applicants respectfully traversed arguing, *inter alia*:

(i) neither Morton, WO 95/15338, nor the MS study nor the combination of the two teach or suggest combination treatment of Cpn10 and IFN-β for MS; and,

(ii) administration of a drug at doses which, if not administered in combination with a second, different drug, would be ineffective, is a significantly different fact pattern than "optimizing" an otherwise clinically effective dose.

Only clinically ineffective amounts of IFN-β used

Regarding (ii), Applicants have respectfully submitted that administering a drug at dosages which, if not administered in combination with a second, different drug, would be ineffective is a significantly different fact pattern than "optimizing" an otherwise clinically effective dose. Administering a drug at a clinically ineffective dose is not merely "optimizing a workable range" by routine experimentation, which was the situation in the cited In re Aller.

Also, as declared by Dr. Johnson in her supplementary declaration, there was no understanding or teachings in the art at the time of the invention to lower an otherwise toxic (side effect-producing) to a *clinically ineffective* dose of IFN-β, and then combine the lower, *clinically ineffective* dose of IFN-β with any compound, e.g., cpn10, to realize an effective therapy for MS. That an otherwise *clinically ineffective* dose of IFN-β could be effective if co-administered with cpn10 was discovered for the first time by the inventors of this claimed invention. See, e.g., page 10, of Applicants' October 16, 2006, response, and Dr. Johnson's expert declaration.

Pending claim 1 is expressly limited to a suboptimal amount of IFN-β which "is not effective if administered alone to the individual". Applicants maintain that this limitation clearly limits the claimed methods to using a "clinically ineffective dose" of IFN-β.

However, the Office remained concerned that the pending claim language regarding "clinically ineffective" dosages might not be a sufficiently clear limitation in the pending claims (see, e.g., page 4, lines 8 to 10, of the Final OA).

To address these concerns and to facilitate prosecution of this application, and to clarify that the claimed methods are expressly limited to using only a clinically ineffective, suboptimal amount of IFN-β which "is not effective if administered alone to the individual", Applicants amend the claims as submitted herein; "suboptimal amount" is replaced with "clinically ineffective amount". The independent claims are also amended simply to clarify this point.

The Office alleged that because the MS study discloses reduced dosages of IFN-β to reduce toxicity, the MS study with the Morton, WO 95/15338, teaching would make the instant invention obvious over prior art (see, e.g., the paragraph spanning pages 3 to 4, of the Final OA).

However, Applicants assert that there was no understanding or teaching in the art at the time of the invention to lower an otherwise toxic (side effect-producing) and clinically effective dose of IFN-β and then combine a lower, clinically ineffective dose of IFN-β with Cpn10 to realize an effective therapy for MS. This was discovered for the first time by the inventors of this claimed invention.

Applicants further respectfully assert that administering a drug at dosages which, if not administered in combination with a second, different drug, would be ineffective is a significantly different fact pattern than "optimizing" an otherwise clinically effective dose. Administering a drug at a clinically ineffective dose is not merely "optimizing a workable range" by routine experimentation, which was the situation in In re Aller (see, e.g. page 3, 3rd paragraph to page 4, 1st paragraph of the Final OA). This is the case regardless as to whether the MS study discloses dosages of IFN-β of 1.6 and 8 MIU; noting the present invention discloses dose ranges of 1 to 10 MIU, or 4 to 6 MIU, of IFN- β). The fact stands that the MS study in light of Morton, WO 95/15338, does not teach or even provide a hint that clinically ineffective dosages of IFN- β can be combined with Cpn10 to successfully treat MS.

Accordingly, because neither Morton, WO 95/15338, nor the MS study taught or suggested administering IFN-β in a combination therapy where the IFN-β is administered at dosages which would be *clinically ineffective* if IFN-β were given alone, e.g., doses that do not produce

IFN-β–induced side effects in the individual, neither cited reference alone or in combination teaches or suggests the claimed invention.

The Art Teaches Away from the Invention

Applicants respectfully submit that the cited art teaches away from the invention as claimed. The Supreme Court in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727, 12 (2007) recently addressed the importance of a teaching away in considering obviousness, reiterating that "...when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious, citing United States v. Adams, 383 U.S. 39, 40, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966).

Jeffrey (2004)

Applicants respectfully submit that Jeffrey (2004) Neurology 63 (Suppl 6):S41-46 (hereinafter "Jeffrey") (submitted with the Rule 132 declaration) teaches away from this claimed invention. Please see paragraph 6 of the enclosed Rule 132 expert declaration of Dr. Barbara Johnson, dated 27 October 2005 (submitted in support of a response, filed on that same day, to a non-Final Office Action dated 27 April 2007). Dr Johnson declared that:

> "... prior to the invention there was no suggestion in the art that combining beta-interferon and chaperonin 10 ... would provide a beneficial benefit. Indeed it is not possible to predict in advance the outcome of combining two agents, and that this is particularly true with autoimmune diseases such as MS."

Dr Johnson's opinion was further supported subsequent to the invention as evidenced by Jeffrey, which *teaches away* from the invention. Please see paragraph 7 of the declaration, where Dr. Johnson declares *inter alia* that Jeffrey highlights a drawback of using combination therapy for treating MS – which is that (quoting Jeffrey) "the agent added to the primary therapy may have no effect, or, worse, may antagonize the effect of the primary agent" (abstract, lines 7 and 8, of Jeffrey).

The Office has stated "... the complete reading of the article [Jeffrey] does teach away from combination therapy and ...[1]" (emphasis added); see page 6, line 2 to 4 of the Office Action dated 1 February 2006, referring to the claimed combination of chaperonin 10 (cpn10) and IFN-β.

Morton (1998) and Yu (1996)

As explained by Dr. Johnson, the teaching of Morton (1998) *Immunol Cell Biol* 76: 483-496, and Yu et al, 1996, *J. Neuroimmunol* 64: 91-100 (hereinafter "Morton (1998)" and "Yu (1996)", respectively; submitted with the Rule 132 declaration) also taught away from this claimed invention. Dr. Johnson declared that at the time of this invention it was thought (wrongly, as it turns out) that Cpn10 and IFN-β acted against MS via similar immunosuppressive mechanisms (paragraphs 8 and 9, page 3, of the 27 October 2005 declaration). Dr. Johnson noted that Morton (1998) and Yu (1996) clearly described Cpn10 and IFN-β as acting via similar mechanisms at the time of this invention - a scenario which is not predictive of a profound therapy for the treatment of MS. Dr. Johnson declared that if Cpn10 and IFN-β did indeed act by similar mechanisms (as taught by Morton (1998) and Yu (1996)) a practitioner in the field would not have expected that combination of drugs having similar mechanisms would have any co-operative (therapeutic) effect.

In contrast to the state of the art at the time of this invention, as evidenced by Morton (1998) and Yu (1996) (counter to the disclosures of Morton (1998) and Yu), the instant invention is surprising because Cpn10 and IFN-β act via *different* biological mechanisms to co-operatively reduce MS symptoms and decrease relapse frequency (see, e.g., page 12, lines 1 to 4, of the specification), while – just as surprisingly - using a *clinically ineffective* amount of IFN-β (administered with cpn10) to not produce IFN-β–induced side effects. Thus, as declared by Dr. Johnson, at the time of the invention a skilled artisan would not have been able to predict a therapeutic effect upon the combined administration of Cpn10 and IFN-β in treating MS.

Barbero teaches away

Further evidence as to the state of the art can be found in Barbero (2004) "High-dose, frequently administered interferon beta therapy for relapsing-remitting multiple sclerosis must be

[1] In its entirety, this sentence reads "However, the complete reading of the article does teach away from combination therapy and suggests that studies are needed to address the question of whether there is an additive or synergistic effect and the address the long-term safety of the combination."

maintained over the long term: the interferon beta dose reduction study" J. Neurol. Sci. Jul; 222(1-2):13-19 (published five years after this application's priority date) (hereinafter "Barbero", a copy attached with this response), which focuses on reducing IFN-β dose/frequency in patients with stable disease in order to improve compliance and convenience. However, Barbero found that patients that took reduced dosages of IFN-β were more susceptible to manifesting larger and new MRI lesions (i.e., an increase in MS incidents) compared to those patients who continued with the higher dose regime (see page 16, first paragraph of section "3.2 *MRI results*"). Barbero concluded that their results demonstrated that higher dosages and frequency of administration of IFN-β brings about a better clinical response in treating MS ("our study showed the negative effects of reducing IFN beta dose …") (see page 17, the "Discussion" section), and that "[t]he reduction of IFN beta-1b dose or frequency of administration frequency is not advisable even in patients with a prolonged absence of clinical and MRI signs of disease activity" (last sentence of the "Discussion" section, page 18, 1st column, 3rd paragraph, of Barbero). Thus, Barbero further evidences that the state of the art, even years after the priority date of this invention, teaches away from this invention.

Arnason and Durelli

Even as late as six years after the priority date of this application, the state of the art continued to teach away from this invention, for example, as evidenced by Arnason (2005) "Long-term experience with interferon beta-1b (Betaferon®) in multiple sclerosis", J. Neurol. 252 [Suppl 3]:III/28-III/33) (hereinafter "Arnason"); the abstract of Durelli (2005) "The importance of maintaining effective therapy in multiple sclerosis", J. Neurol. 252 [Suppl 3]: III/38-III/43 (copies attached herein). These two studies focus on increasing the dosage of IFN-β to achieve increased clinical efficacy and convincingly teach away that lower dosages of IFN-β would successfully prevent relapsing-remitting MS as well as acute MS.

In particular, Arnason taught that "the high dose treatment reduced the frequency and severity of attacks and markedly reduced disease severity as measured by MRI." In other words, the increase in IFN-β dosages will likely result in increased efficacy of treating MS (see, e.g., page 29, 2nd paragraph). Durelli taught that high-dose, high-frequency IFN-β treatment offers greater therapeutic benefit, in terms of clinical and MRI outcome measures compared with low-dose, low-frequency treatment; and stated that "the data from this study suggested that patients who have

'stable' disease (i.e. no evidence of clinical MRI disease activity) during long-term treatment with IFN-β-1b 250μg, who are subsequently treated with low-dose, once-weekly IFN-β-1a 30μg, are more likely to experience relapses, disease progression or MRI activity compared with those remaining on IFN-β-1b 250 μg.

Taken together, these disclosures evidence that the state of the art at the time of this invention taught away from the claimed invention; for example, these documents provide a clear indication that the state of the art believed that a high-dose, high-frequency therapy of IFN-β should be used and maintained to achieve the optimal therapeutic benefit for MS patients.

Kerkhoven

On a separate point, the Office cited In re Kerkhoven (205 USPQ 1069, CCPA 1980) in the Office Action dated 1 February 2006 and provided the following excerpt: "It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a combination that is to be used for the very same purpose: the idea of combining them flows logically from their having been individually taught in the prior art".

Applicants submit that a clinically ineffective dose of IFN-β was not taught in the prior art; and indeed the at the time of the invention the state of the art taught that such combination may be ineffective in treating MS, and the state of the art encouraged a high-dose, high-frequency use of IFN-β for treating MS (as discussed above). Accordingly, Applicants respectfully submit that because the holding of In re Kerkhoven is related to a different set of circumstances it does not support an obvious rejection for this invention.

In light of the above arguments and proposed amendments, the Applicants respectfully assert that this section 103 rejection can be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §103(a). In view of the above, claims in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. **284502000600**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-5133.

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Respectfully submitted,

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High-dose, frequently administered interferon beta therapy for relapsing–remitting multiple sclerosis must be maintained over the long term: the interferon beta dose-reduction study

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Abstract

Long-term trials have demonstrated the continued efficacy of interferon (IFN) beta treatment in patients with relapsing–remitting (RR) multiple sclerosis (MS) during prolonged administration.

The objective of the work was to evaluate the effects of reducing IFN beta administration frequency and total weekly dose in patients with RR MS who have achieved clinical and MRI disease activity stabilization during long-term IFN beta-1b treatment. Prospective 1-year follow-up of 27 RR MS patients on long-term 250 μg every other day (standard dose) IFN beta-1b treatment were randomized either to gradually reduce dose to 30 μg once-a-week IFN beta-1a (13 patients), or to continue on IFN beta-1b standard dose (14 patients).

We found significant differences in the two group of patients. In the group of patients continuously treated with IFN beta-1b standard dose, 79% remained relapse free compared to 23% in the group receiving once-weekly IFN beta-1a ($p=0.006$). The number of patients without new PD/T2 lesions was higher in the group of patients continuously treated with IFN beta-1b standard dose (77%) compared to the once-weekly IFN beta-1a group (23%) ($p=0.04$). IFN beta is a long-term treatment for MS. The reduction of IFN beta-1b administration frequency and dose is not advisable even in patients free from clinical and MRI disease activity for many years.

Keywords: Interferon beta-1a; Interferon beta-1b; Interferon beta dose reduction; Multiple sclerosis; Relapsing–remitting; Relapses; Disease progression; Magnetic resonance imaging

1. Introduction

Interferon (IFN) beta was the first drug registered for treatment of relapsing–remitting (RR) multiple sclerosis (MS). Placebo-controlled, multicenter clinical studies have demonstrated the therapeutic efficacy of IFN beta-1a, 6 million international units (MIU) (30 μg) intramuscularly (im) once weekly [1], IFN beta-1b, 8 MIU (250 μg) subcutaneously (sc) every other day [2] and IFN beta-1a, 6 or 12 MIU (22 or 44 μg) sc three times per week [3]. In these studies, treatment with IFN beta resulted in reduction of the exacerbation rate or reduced disability progression as evaluated by the expanded disability status scale (EDSS) [4]. In addition, IFN beta reduced the occurrence of new and enhancing lesions on brain magnetic resonance imaging (MRI) scans [3,5 6 7 8]. Consequently, IFN beta has become the most widely used treatment for patients with RR MS.

Patient compliance is an important issue for any long-term therapy and should be carefully considered when selecting such therapies. Two recent studies, INCOMIN [11] and EVIDENCE [12], both demonstrated significant clinical and MRI benefits for frequently administrated IFN beta, when compared to once a weekly administration. The treatment of MS with IFN beta requires, therefore, multiple weekly parenteral administrations for an, as yet, undetermined length of time. Some patients may find that such a treatment regimen is difficult to cope with over a long period. This requirement for several weekly parental injections, possibly for many years, may result in patients becoming frustrated and may ultimately drive them to the dangerous and uncontrollable decision to reduce adminis-

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tration frequency without consulting their physicians. In addition, higher doses of IFN beta may be needed during the first years of treatment to induce the expected immunological [8,9] and clinical effects [1,4,10]. Once these effects are achieved, one can hypothesize that maintaining them might be possible using lower doses.

These considerations prompted us to try to identify the minimum effective dose and administration frequency for IFN beta, by slowly reducing both the dose and the number of weekly administrations. Reducing the dose of IFN beta may, however, expose patients to the risk that the disease may become active again. We therefore designed this dose reduction study to include careful monitoring of the potential clinical and MRI effects associated with IFN beta dose reduction.

2. Patients and methods

2.1. Study design

This was a randomized study performed in the Department of Neurosciences at Torino University. Patients, prospectively followed up in our center and who met the inclusion criteria, were enrolled between January 1999 and January 2000 (Fig. 1). To be included in the study, patients had to be diagnosed with definite RR MS [13], with an EDSS score of 1.0–4.0. In addition, they had to be in receipt of IFN beta-1b (8 MIU every other day) treatment for at least 36 months, with no relapses or disease progression (defined as an increase in EDSS score of >0.5 points) during the previous 24 months, and with no MRI signs of disease activity during the previous year. MRI scans performed 1 year (± 30 days) and immediately before starting the dose reduction protocol (study baseline) were used to assess disease activity. In the first scan, the absence of enhancing lesions on post-gadolinium (Gd) T1-weighted sequences was used to indicate lack of disease activity. For the scan obtained at study baseline, patients were considered free of disease activity if there were no Gd-enhancing lesions and no enlarged or new proton density (PD)/T2 lesions when compared to the previous scan.

Each patient included in the study was assigned a code that was forwarded to the statistical team at the Department of Public Health, Torino University, who randomly assigned patients to one of two treatment groups. In the first group (group A), patients would continue with IFN beta-1b at the standard dose (8 MIU, i.e., 250 μg sc, every other day) (14 patients; 11 women), while in the second group (group B), patients would slowly reduce their IFN beta-1b dose, until they were receiving once-weekly 6 MIU (30 μg im) IFN beta-1a (13 patients; 10 women).

Patients reducing their dose from IFN beta-1b to once-weekly IFN beta-1a followed a strict dose reduction protocol. IFN beta-1b was reduced from 8 MIU every other day to 8 MIU three times per week for the first two weeks; then, for the third and fourth week, to two weekly administrations of 8 MIU; then to 4 MIU twice weekly (fifth and sixth week). From week seven onwards, patients received once-weekly IFN beta-1a. Patients in the two groups were followed up for 1 year with clinical, laboratory and MRI evaluations all being performed. Written consent was obtained from all patients.

2.2. Clinical and laboratory assessments

Neurological assessments were performed on all patients every 3 months or in cases of relapse. The investigating physician, therefore, objectively confirmed all relapses. Relapses, when characterized by a score of three or more in at least one, or of two in at least three, of the functional systems of the Kurtzke scale [4] could be treated with a standard regimen of high-dose intravenous methylprednisolone (1 g/day for 10 days).

All patients underwent laboratory tests, including hematological, immunological, liver, thyroid and kidney function

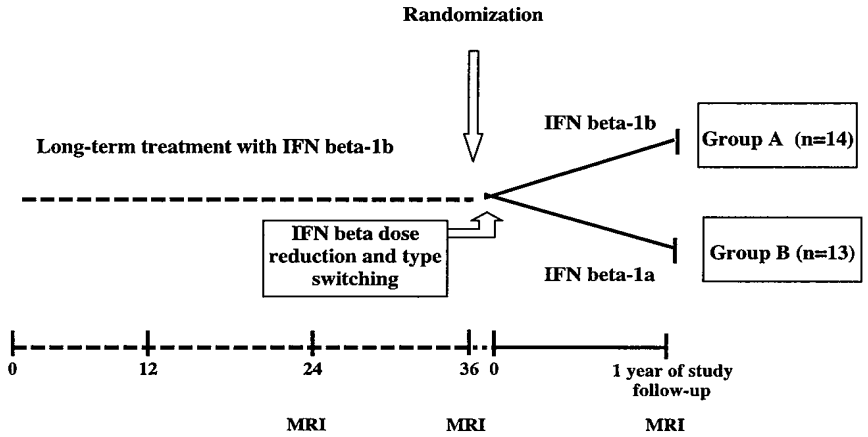

Fig. 1. Trial profile.

tests. Patients were tested for IFN beta neutralizing antibodies (NAb) at baseline and at the end of the study. The presence of NAbs was determined by the Department of Experimental Medicine and Pathology, Virology Section, University "La Sapienza", Roma, Italy. Antibody titers were determined in a neutralization bioassay against 10 IU of IFN beta [14]. Titers of ≥ 20 neutralizing units/ml were considered positive.

The primary clinical outcome measure was the number of patients remaining relapse free. The secondary clinical outcome measures were the number of patients requiring either corticosteroid therapy or hospitalization, relapse rate, the number of patients without progression of disability (defined as an increase in EDSS score of ≥ 1.0 point, sustained for at least 3 months). All clinical outcomes were assessed in an open-label manner.

2.3. MRI analysis

Brain MRI scans were performed 1 year before the study ($\pm$ 30 days), at study baseline, and after 1 year of follow-up. Scans were obtained using a scanner operating at 1.0 T (Siemens Impact, Erlangen, Germany). Brain MRIs were performed according to a protocol that required strict positioning techniques using coronal, axial and sagittal localizers (scout scans). Axial scans were composed of 24 contiguous axial slices acquired with a 5-mm slice thickness, a 256×256 matrix, and a 250 FOV. During all MRI sessions, the following sequences were performed: PD/T2-weighted dual echo conventional spin echo (CSE) (reception time [TR]: 2000–2400; echo time [TE]: 20/80 ms); T1-weighted (TR: 720 ms; TE: 20 ms) pre- and post-contrast. The standard dose (0.1 mmol/kg) of Gd contrast agent was administered for the post-contrast T1-weighted scan, which was obtained 5 min after intravenous Gd administration.

The primary MRI outcome measure was the number of patients without new PD/T2 lesions. Secondary MRI outcome measures were the mean number of new PD/T2 lesions, the number of patients with no enlargement of existing PD/T2 lesions [13], the mean number of enlarged lesions, the number of patients without enhancing T1-lesions, the mean number of enhancing lesions [15], the number of patients without PD/T2-weighted combined active scans (scans with either enlarged or new PD/T2 lesions), the number of patients without PD/T2 and T1-weighted combined active scans (scans with either enlarged or new PD/T2 or enhancing lesions), PD/T2 and T1-weighted burden of disease (BOD). PD/T2 BOD is the total area of brain hyperintense white matter lesions on PD/T2 scans, and T1-weighted BOD is the total area of brain hypointense white matter lesions on post-Gd T1-weighted scans.

A neuroradiologist and a neurologist, working together, evaluated the MRI scans by consensus. Both were blinded to the patient's clinical characteristics and treatment. Hyperintense lesions were recorded on the original films of PD/T2 scans. These were counted, and then area measurements were performed by a single evaluator [16] with a SUN Microsystems workstation (Solaris 8) using a semiautomatic local thresholding technique. The software used was Dispimage, developed by D. Plummer (University College, London, UK) [17]. Hypointense lesions were marked, counted and their area measured using the same software used for hyperintense lesions but on post-Gd T1-weighted scans.

2.4. Statistical analysis

For dichotomous variables, the cumulative incidence was calculated and significance of difference tested with the Fisher's exact test; for continuous normally distributed variables, mean and standard deviation were calculated and significance tested with parametric tests (Student's t test). Differences in percentage changes from baseline of BOD were tested with Wilcoxon's rank sum test. Time to first relapse was calculated using the life-table method and significance tested with the log-rank test.

3. Results

Four patients were excluded from randomization because their MRI scan at study baseline demonstrated signs of disease activity. Twenty-seven RR MS patients fulfilling the inclusion criteria were randomized and all patients completed 1 year of treatment and follow-up, with no protocol deviations. There were no differences in demographic, clinical and MRI parameters between the two randomized groups before starting IFN beta therapy and at study baseline (Table 1).

3.1. Clinical results

Outcome measures were better in group A (patients continuously treated with IFN beta-1b standard dose) than in group B (patients who reduce their IFN beta-1b dose until they were receiving once-weekly IFN beta-1a) (Table 2). In group A, 79% remained relapse free compared to 23% in group B ($p=0.006$). Relapse rate was significantly lower in group A compared to group B ($p=0.03$). Similar differences were observed in the requirements for corticosteroid therapy or hospitalization with 21% of patients in group A requiring corticosteroid therapy compared to 61.5% in group B ($p=0.04$) while the steroid-treated relapse rates were 0.2 and 0.7, respectively ($p=0.03$).

Fig. 2A shows the longitudinal distribution of relapses during the year of follow-up in the two groups. The first relapse occurred in one patient whose dose was reduced to once-weekly IFN beta-1a, 50 days after beginning chronic IFN beta-1a treatment. No relapses occurred during the period of IFN beta-1b dose reduction. Time to first relapse was significantly shorter in the group of patients receiving once-weekly ($p=0.001$) IFN beta-1a (Fig. 2B). The EDSS score was slightly (15%) increased in group B, while it

Table 1
Demographic, clinical and MRI characteristics of the two groups

	Group B ($N=13$)	Group A ($N=14$)
Before starting IFN beta treatment		
Women	10	11
Age at entry (mean ± S.D.)	34.1 ± 6.8	32.9 ± 6.9
Disease duration (mean ± S.D.)	10.5 ± 3.4	10.1 ± 3.3
Annualized relapse rate (mean ± S.D.)	1.2 ± 0.6	1.1 ± 0.4
EDSS (mean ± S.D.)	2.4 ± 0.95	2.5 ± 0.95
Before starting the randomized study (baseline)		
Annualized relapse rate	0	0
EDSS (mean ± S.D.)	2.4 ± 0.95	2.5 ± 0.91
IFN beta treatment duration (months) (mean ± S.D.)	36.9 ± 1.03	37.2 ± 1.05
Baseline PD/T2-weighted BOD (mm^2) (mean ± S.D.)	2541.5 ± 660.6	2602.1 ± 613
Baseline PD/T2-weighted BOD (mm^2) (median)	2500	2525
Baseline T1-weighted BOD (mm^2) (mean ± S.D.)	235.5 ± 106.9	225.1 ± 151.4
Baseline T1-weighted BOD (mm^2) (median)	290	173.4

Group A = patients continuously treated with IFN beta-1b; Group B = patients who underwent dose reduction to once-weekly IFN beta-1a; IFN = interferon; EDSS = expanded disability status scale; PD/T2-weighted = proton density/T2-weighted magnetic resonance imaging scan; BOD = burden of disease; T1-weighted = T1-weighted magnetic resonance imaging scan.

remained almost unchanged in group A. The EDSS score at the end of the follow-up period was not, however, significantly different in the two groups. In addition, 23% of patients undergoing dose reduction to once-weekly IFN beta-1a developed sustained disability progression compared to none in the group of patients continuously treated with IFN beta-1b standard dose. The proportion of patients with sustained disability progression was not, however, significantly different in the two groups.

At the end of the study, six patients were NAb positive. Two were in group B. Both patients were NAb positive at study baseline, and both had active MRI scans and relapses during the year follow-up. The other four NAb positive patients were in group A. All NAb positive patients in group A were positive at baseline with the exception of one, who became positive at the end of the study. Two of these patients were free of clinical and MRI activity during the year of follow-up; the third one had a relapse; the fourth MRI activity. By comparing the occurrence of clinical or MRI activity in Nab positive and Nab negative patients no significant difference was observed.

3.2. MRI results

The primary MRI outcome measure favored the patients continuously treated with IFN beta-1b standard dose (Table 2). In this group, 77% of patients remained free from new PD/T2 lesions compared to 23% in those receiving once-weekly IFN beta-1a ($p=0.04$). Many secondary MRI outcome measures were also significantly better in this group of patients compared to those reduced to once-weekly IFN beta-1a. These included the proportion of patients remaining free of new enhancing lesions (79% vs. 38.5%; $p=0.04$), the proportion of patients without PD/T2-weighted combined active scans (64% vs. 23%; $p=0.04$), and the proportion of patients without PD/T2 and T1-weighted combined active scans (64% vs. 15%; $p=0.01$).

The PD/T2 BOD (Table 2) did not significantly change from baseline in group A, with a median percentage change of −0.9%, while it significantly increased from baseline in

Table 2
Clinical and MRI outcome measures

	Group B ($N=13$)	Group A ($N=14$)
Clinical outcome measures		
Patients without relapses	3*	11
Relapse rate (mean ± S.D.)	0.9 ± 0.6**	0.2 ± 0.4
Number relapses	12	3
Patients treated with corticosteroid therapy	8#	3
Corticosteroid-treated relapse rate (mean ± S.D.)	0.7 ± 6.3**	0.2 ± 4.2
EDSS (mean ± S.D.)	2.6 ± 1.74	2.5 ± 0.91
Patients with sustained disability progression	3	0
MRI outcome measures: PD/T2-weighted scans		
Patients without new lesions	3#	9
Patients without enlarging lesions	8	13
Patients without combined PD/T2 (new + enlarging PD/T2)	3#	9
New lesions (mean ± S.D.)	1.92 ± 1.32*	0.57 ± 0.94
Enlarging lesions (mean ± S.D.)	0.69 ± 0.95	0.21 ± 0.8
BOD percent change from baseline (median)	6.7##	−0.9
MRI outcome measures: T1-weighted scans		
Patients without Gad-enhancing lesions	5#	11
Patients without combined T1 + PD/T2	2###	9
Gad-enhancing lesions (mean ± S.D.)	0.92 ± 0.95#	0.35 ± 0.74
BOD percent change from baseline (median)	0.4	−1.4

The difference with the group of patients continuously treated with standard dose IFN beta-1b is indicated when significant.
Group A = patients continually treated with IFN beta-1b; Group B = patients switched to once-a-week IFN beta-1a; IFN = interferon; EDSS = expanded disability status scale; MRI = magnetic resonance imaging; PD = Proton Density; Gad = gadolinium; BOD = burden of disease.
* $p=0.006$.
** $p=0.03$.
\# $p=0.04$.
\#\# $p=0.0015$.
\#\#\# $p=0.01$.

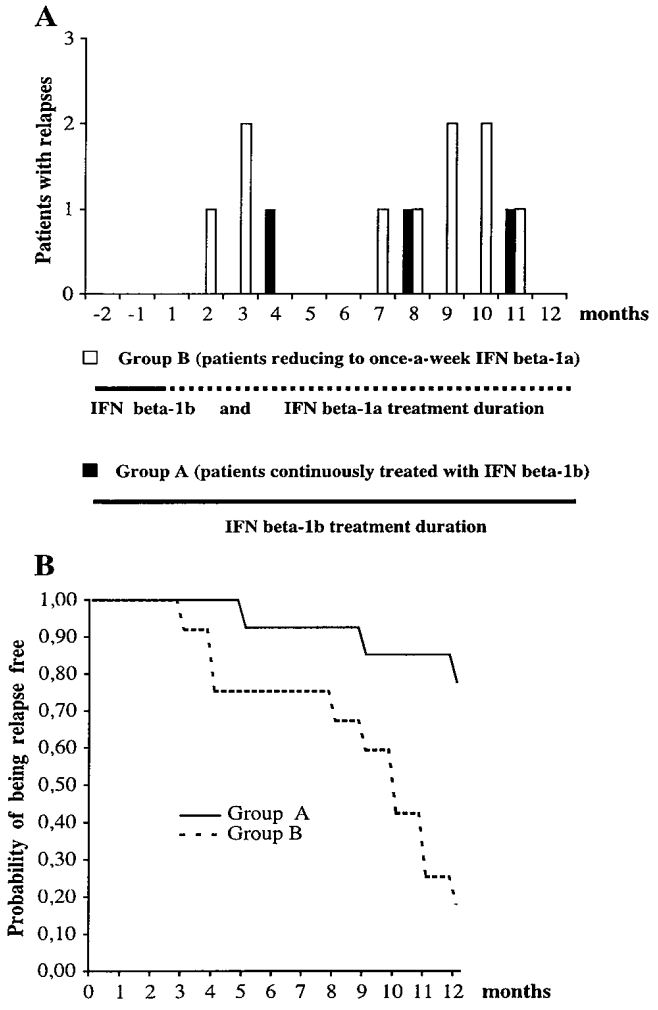

Fig. 2. Longitudinal distribution of relapses (A), and time to first relapse (B) during the year of the study. Time to first relapse was significantly shorter in the group of patients receiving once-weekly ($p<0.001$) IFN beta-1a. Group A, patients continuously treated with IFN beta-1b standard dose); group B, patients who reduce their IFN beta-1b dose until they were receiving once-weekly IFN beta-1a.

group B, with a median percentage change of +6.7% ($p=0.0015$). The difference in percentage change in PD/T2 BOD was also statistically significant between the groups ($p=0.0047$). The T1-weighted BOD (Table 2) did not significantly change from baseline in both patient groups and the difference in percentage change between the groups was also not statistically significant.

4. Discussion

Recent studies or metanalyses comparing different doses or frequency of administration of type I interferon [3,18–20] showed a dose–response curve for clinical efficacy in RR MS. Direct clinical and MRI comparisons [11,12] of two different doses and schedules of administration of IFN beta have demonstrated that a higher dose and frequency of administration brings about a better response. The INCOMIN trial [11] demonstrated that, over the long term, both the proportion of relapse-free patients and of those remaining free from new T2 lesions on MRI scans were significantly higher in the patients treated with 8 MIU (250 μg) IFN beta-1b every other day than in those treated with 6 MIU (30 μg) once-weekly IFN beta-1a. The EVIDENCE trial (comparing IFN beta-1a given either subcutaneously, 44 μg, three times per week, or intramuscularly, 30 μg, once a week) [12] confirmed these results over the short term. These studies strongly indicate that IFN beta given at higher doses several times per week has a greater clinical and MRI efficacy compared to the once-weekly administration schedule. A dose–response effect for IFN beta has been reported in pharmacologic study [21–24] and in the therapy of other diseases such as acute and chronic hepatitis, leukemia, and other malignant disease [25,26].

All these studies demonstrate that type I IFN treatment must be given at high dose and with frequent weekly parenteral injections. However, when selecting a long-term treatment requiring several weekly injections, the patient's compliance must be considered. After many years of treatment, a patient with a good clinical response may be induced to reduce the administration frequency hoping to maintain the achieved disease stabilization even with a lower number of weekly injections. The aim of this study was, therefore, to evaluate whether it might be possible to reduce the frequency of administration (and therefore the total weekly dose) of IFN beta after a long period of disease stability. Although no published definition of disease stabilization during IFN beta treatment is available, in our opinion, 2 years with no relapses or EDSS progression and 1 year without MRI signs of disease activity is an acceptable definition of disease stabilization. This study is the first to examine the clinical and MRI effects of a progressive reduction of the administration frequency and of the dose of IFN beta compared to a parallel control group of patients continuously treated with IFN beta-1b standard dose.

Our study showed the negative effects of reducing IFN beta dose and frequency of administration on both clinical and MRI outcome measures. Most clinical parameters worsened in the patients who underwent dose reduction to once-weekly IFN beta-1a. MRI analysis confirmed the clinical results. The proportion of patients with Gd-enhancing lesions, reflecting new or reactivated brain inflammatory events, with local breakdown of the blood–brain barrier [27], was greater in the group of patients receiving once-weekly IFN beta-1a. Gd-enhancing lesions, however, are not a sensitive marker of disease activity in a study where scans were performed yearly. Gd enhancement is of short duration, lasting 30–45 days and, therefore, reflects only disease activity in the 30–45 days preceding the MRI scan [28,29]. A more accurate MRI outcome measure reflecting overall disease activity in the interval between two yearly

MRI scans is the occurrence of new or enlarging PD/T2 lesions and the quantitative measurement of PD/T2 BOD [29]. Most PD/T2 lesions do not disappear and their cumulative count or area therefore reflects disease activity accrued over time. We therefore chose the number of patients without new PD/T2 lesions as the MRI primary outcome measure.

The occurrence of PD/T2 and Gd-enhancing lesions is probably a reflection of acute inflammatory and demyelinating damage and its evaluation is therefore an important measure of subclinical disease progression. PD/T2 MRI parameters are, however, poorly correlated with disability progression, which is more likely to be the clinical counterpart of progressive axonal damage [30].

Our study may draw criticism because it was conducted on a small patient sample, followed up in a single center, and evaluated by unblinded clinical investigators. In our study, however, analysis of MRI scans, performed by blinded investigators, confirmed the clinical results. Data from this study so clearly favors the group of patients continuously treated with every-other-day IFN beta-1b compared to those receiving once-weekly IFN beta-1a, that we would recommend most strongly that IFN beta-1b treatment at a regimen of multiple weekly administrations must be maintained in the long term. The reduction of IFN beta-1b dose or frequency of administration is not advisable even in those patients with a prolonged absence of clinical and MRI signs of disease activity.

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Long-term experience with interferon beta-1b (Betaferon®) in multiple sclerosis

Abstract The interferon beta-1b (IFNβ-1b, Betaferon®/Betaseron®) molecule was cloned some 20 years ago. In a pilot dose-finding trial involving 30 multiple sclerosis (MS) patients, the 10 MS patients receiving 250 μg (8 MIU) IFNβ-1b every other day at 6 months showed a reduced attack frequency relative to 6 patients receiving placebo. Based on these extremely preliminary results a Phase III placebo-controlled trial was undertaken. Treatment with IFNβ-1b was shown to reduce attack frequency and severity and to markedly reduce magnetic resonance imaging-(MRI) measured activity and disease burden. IFNβ-1b therapy was subsequently shown to reduce MRI activity within 2 weeks of starting treatment. The benefits of treatment with IFNβ-1b observed in the original pivotal study are maintained in the longer term, with consistent treatment effects seen after 5 years. IFNβ-1b has subsequently been shown to reduce accumulation of disability in MS patients with early active secondary progressive disease, to increase cerebral metabolism, and to improve cognitive performance.

IFNβ-1b therapy is generally well tolerated. Classical systemic side effects related to all beta interferons can effectively be managed by dose escalation, and the use of an autoinjector minimises injection site reactions.

About one-third of MS patients receiving IFNβ-1b develop anti-interferon antibodies, typically within the first year of therapy. These antibodies have variable titres that fall with time and ultimately disappear in most patients. The clinical consequences of the presence of antibodies are presently unclear and inconsistent – some patients without antibodies respond poorly to treatment, whereas others with high-titre antibodies respond well to treatment. It is possible that immune complexes formed when anti-interferon antibodies encounter IFNβ may enhance some of the immunomodulatory actions of the drug by improving CD8 cell-mediated suppressor function. Until the clinical relevance of antibodies is better understood, treatment decisions should be based on clinical grounds only.

Key words interferon beta-1b · multiple sclerosis · neutralising antibodies · efficacy · clinical response

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Introduction

Human interferon beta-1b (IFNβ-1b, Betaferon®/Betaseron®) was cloned in *E coli* in 1980. As bacteria lack the ability to glycosylate proteins, the protein was not glycosylated. The cysteine residue at position 17 was replaced with a serine residue to ensure the stability of the molecule [16] and the N-terminal methionine residue was deleted. An IND for the modified product – Betaseron® – was submitted to the FDA in 1983 and, following an extensive clinical development programme, the product has now become one of the most widely used therapies for multiple sclerosis (MS). Long-term experience with this therapeutic agent has revealed its beneficial effects on clinical and MRI measures of MS, with acceptable and usually transient side effects. This article reviews the findings from the pilot and Phase III trials of this compound.

IFNβ-1b increases CD8 T cell function in MS

In active MS, CD8 regulatory cell function is defective [2]. This means that the inflammatory response is not suppressed, and thus, activated immune cells may cause "bystander" damage of the CNS or an autoimmune response may attack CNS components. Class I interferons are thought to exert a therapeutic effect in MS partly by activating CD8-type T cells [19, 20]. Indeed, in one pilot study, treatment with IFNβ-1b increased CD8 cell-mediated suppressor function in MS patients in a dose-dependent manner (Table 1) [18]. Placebo had no significant effect on CD8 function, whereas the 250 μg dose of IFNβ-1b increased CD8 function in MS patients to levels approaching that of patients without MS. Given that the lower dose of IFNβ-1b showed a lesser effect on CD8 suppressor cell function, even these early data highlight that adequate dosing is an important issue with IFNβ-1b treatment.

Clinical trials of IFNβ-1b

Early studies showed that the route of IFNβ-1b administration was not critical – the effect on markers of IFNβ-1b activity was the same whether administration was subcutaneous, intra-muscular or intravenous [5]. Subcutaneous administration was therefore chosen as the most convenient option for a pilot dose-finding trial of IFNβ-1b in 30 patients with MS [15]. During the initial dose-finding period (24 weeks), 5 groups of 6 patients each were treated with 25, 125, 250 or 500 μg (0.8, 4.0, 8.0 or 16 MIU) IFNβ-1b or placebo 3 times weekly.

The results from the initial dose-finding period were deemed promising. There was a dose-related trend in the reduction of exacerbation frequency. However, patients given the highest dose of IFNβ-1b (500 μg) experienced side effects that led to dose reduction or drop-out within a short time-frame. Four of these patients subsequently received the 250 μg dose. The 10 patients receiving the 250 μg dose of IFNβ-1b at the end of the study (6 patients initially randomised to this dose plus 4 patients switched from the 500 μg dose group) had a reduced attack frequency compared with the 6 patients receiving placebo, although this result did not achieve significance, perhaps due to the short duration of the study coupled with the relatively small number of patients. IFNβ-1b was generally well tolerated, and the side-effect profile showed some relationship with dose administered. On the basis of the results of this study, a dose of 250 μg IFNβ-1b every other day rather than 3 times weekly was selected for further investigation on the grounds that a slightly greater treatment effect might be desirable.

A Phase III trial was conducted with MS patients using doses of 50 μg and 250 μg IFNβ-1b [12]. The higher dose treatment reduced the frequency and severity of attacks and markedly reduced disease severity as measured by MRI [22]. These pivotal trial results led to the approval, in 1993, of IFNβ-1b (Betaseron®) as the first therapeutic agent for relapsing-remitting MS (RRMS).

Final data from the same study was based on patients who had received treatment for up to 5 years [13]. These results demonstrated that the beneficial effect on relapse rate and MRI burden of disease observed in patients receiving IFNβ-1b 250 μg during the first 2 years of the study was maintained over the longer term. In patients receiving treatment, year-on-year relapse rates were reduced by approximately one-third, relative to placebo, and severe attacks by approximately 50% [13]. A subsequent post-hoc analysis revealed that the beneficial effect of IFNβ-1b on relapse frequency had rapid onset, with an effect being observed as early as the second month of treatment [3]. There was also a clear-cut effect of IFNβ-1b on MRI burden of disease (Fig. 1). The percentage increase in MRI lesion burden in the placebo arm was approximately 5-fold higher than that seen in the higher dose IFNβ-1b group, and even the lower dose reduced MRI lesion burden substantially.

Subsequently, IFNβ-1b has been shown to reduce the accumulation of disability in patients early into sec-

Table 1 CD8 T cell function in MS and after treatment with IFNβ-1b [18]

Patients	Number of observations	Percentage suppression of CD8 T cells
Controls (no MS)	94	37.2±2.5
MS at baseline	31	17.5±4.2
Placebo	41	19.9±3.3
IFNβ-1b 50 μg	45	24.8±3.8
IFNβ-1b 250 μg	49	32.1±3.6

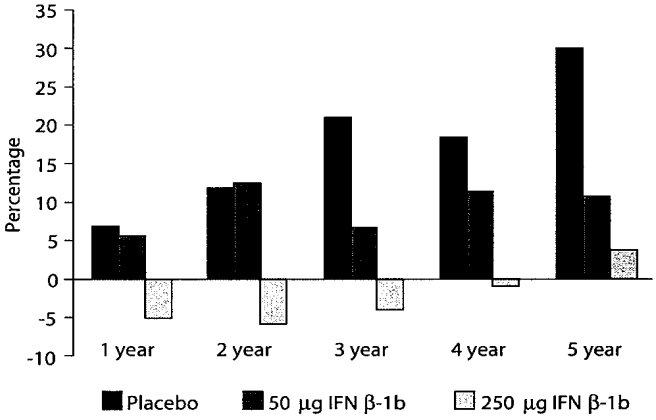


Fig. 1 Cumulative MRI lesion burden median change (from [13] with permission of Lippincott Williams & Wilkins)

ondary progressive MS (SPMS). In a randomised, placebo-controlled trial in 718 patients with SPMS [7], IFNβ-1b treatment significantly increased the time to confirmed progression of disability, with a delay of 9–12 months over a 2- to 3-year period. This effect was observed regardless of baseline Expanded Disability Status Scale (EDSS) score and the presence of superimposed relapses. Significant effects were also observed for IFNβ-1b-treated patients on secondary clinical outcome measures including overall relapse rate and severity, and hospital admissions, relative to placebo-treated patients. IFNβ-1b treatment also produced a substantial and sustained reduction in the accumulation of new inflammatory disease foci over a period of at least 2 years [17]. Serial MRI scans demonstrated a highly significant difference in total lesion volume between treatment groups: the placebo group showed a 15% increase from baseline to final scan, compared with a reduction of 1.6% ($P < 0.0001$) in the IFNβ-1b-treated group. In a subgroup of 125 patients who underwent monthly gadolinium-enhanced and PD/T2-weighted MRI, the number of new or enlarging lesions was also significantly reduced by IFNβ treatment at all time points [17].

In addition to effects on clinical parameters, such as relapse rate, disease progression and MRI parameters, IFNβ-1b has been shown to have a positive effect on cognitive outcome measures. Cognitive impairment is an important contributor to the disability seen in MS. Cognitive deficits can occur early in the course of MS and may therefore have a long-term impact on both patients and their families. Unemployment, social isolation and the need for personal assistance at home are greater in patients with cognitive impairment [25], and such patients have been reported to be at significantly greater risk of suffering from depression [10]. Positron emission tomography (PET) scanning shows that there is a global decrease in metabolism in the brains of patients with MS, which is associated with fatigue [28]. IFNβ-1b increased cerebral metabolism, as measured by MRI spectroscopy beginning 6 months after onset of therapy, and improved cognitive performance in a study involving 30 patients with MS between years 1 and 3 of treatment [23]. In the Wechsler Memory Scale Visual Reproduction – Delayed Recall test – a measure of short-term memory – there was significant improvement in patients receiving 250 μg IFNβ-1b between years 2 and 4 of the study ($P < 0.03$). The effects of IFNβ-1b on cognition did not correlate with changes in disability score, mean MRI lesion area or depression rating score. Similarly, a 1-year study of the effects of IFNβ-1b on cognitive function in 16 patients with RRMS showed improvement in the Wisconsin Card Sort Test, a measure of frontal lobe function, and the Event-Related Potential, a potential measure of cognitive function, relative to pre-treatment performance [9].

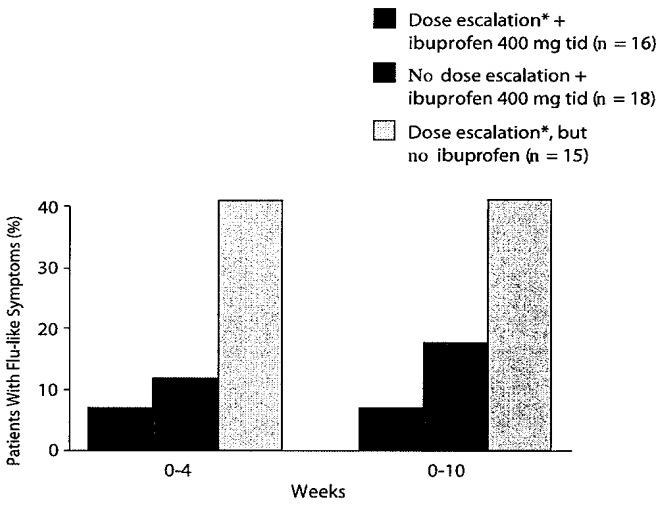
Adverse events with IFNβ

Systemic

Common side effects of IFNβ include flu-like symptoms (fever, chills and fatigue), seen primarily at initiation of therapy and attenuating spontaneously over the first few months of treatment. However, flu-like symptoms at the onset of therapy can be markedly reduced by gradual dose escalation and concomitant non-steroidal anti-inflammatory drug (NSAID) prophylaxis [26]. The dramatic effects of dose escalation in combination with ibuprofen co-medication can be seen in Fig. 2. A dose escalation schedule of 25%, 50% and 75% of full dose over the first 6 weeks is widely implemented [1]. Dosing at night can also be beneficial as patients may be able to sleep through any adverse events.

Injection site reactions

Injection site reactions are a recognised complication of IFNβ use [30, 31]. In the original pivotal IFNβ-1b study, injection site reactions occurred at least once during the study in 81% of patients receiving low-dose IFNβ-1b (50 μg) and 86% of patients receiving standard dose IFNβ-1b (250 μg), compared with 37% of patients receiving placebo [13]. Nevertheless, the frequency of injection site reactions decreased markedly during the first few months of treatment, and after 1 year 50% of patients in the high-dose group reported a reaction [13]. In my experience, approximately 50% of MS patients continue to experience skin reactions during long-term treatment.



*Dose escalation: increase by 64 μg (2 MIU) IFNβ-1b every week

Fig. 2 Managing flu-like symptoms during initiation of IFNβ treatment can be reduced by dose escalation and NSAID co-medication [26]

Injection site reactions may result from contact between skin and subdermal tissue and IFNβ during injection. When the same needle is used to withdraw the reconstituted drug as is being used to administer it, there is a possibility that the exterior surface of the needle will be coated with the drug, thereby increasing skin reactions. Inconsistencies in injection technique may also account for the variation in the frequency of occurrence and the severity of injection site reactions associated with the use of IFNβ. The use of other injection methods, such as an automated injection device, or interferon-free needles (by changing the needle after the drug has been drawn into the syringe), could therefore have a positive effect on injection site reactions.

A recent study has compared the single needle, interferon-free needle and automated injection techniques in 28 patients receiving IFNβ-1b therapy. Compared with the single-needle technique, use of either an automated injection system or interferon-free needle for subcutaneous administration of IFNβ-1b was shown to significantly decrease the number of injection site reactions and increase the number of patients who were free of such adverse effects (Fig. 3) [29].

In line with the results from this study, the current IFNβ-1b prescribing information specifies that IFNβ-1b be administered either with an automated injector, or using the interferon-free needle technique [1]. The frequency and severity of injection site reactions may also be reduced by rotating the site of injection, using different areas of the body for each injection, to ensure that the distance between concurrent injections is maximised and that the injection site has several weeks to recover before being used again.

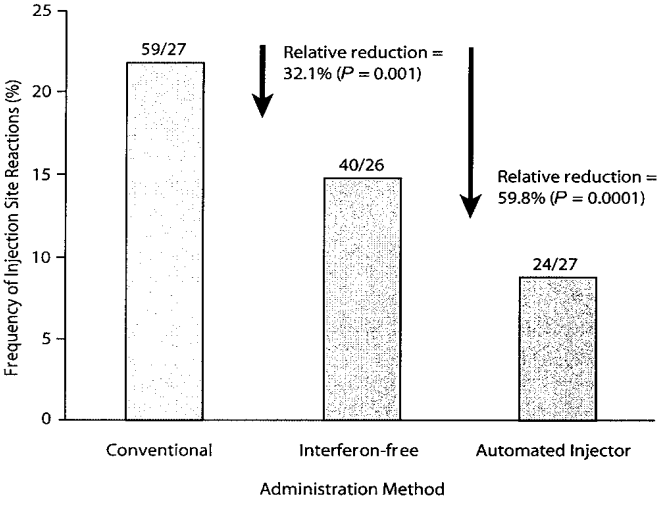


Fig. 3 Significant reductions in the frequency of injection site reactions using automated injection techniques and interferon-free needles [29]

The clinical relevance of antibodies to beta interferon

The clinical importance of the development of antibodies to IFNβ in MS patients remains a controversial issue. In patients with leukaemia or hepatitis treated with interferon alpha, the development of high-titre (> 1:500) antibodies can cause a clear-cut loss of efficacy. By extrapolation, the presence of neutralising antibodies in MS led to the perception that a major loss of efficacy must accompany their appearance [4]. The problem has been that an impact of antibodies on the treatment response in MS has not been clearly or consistently found. In the clinic, some patients with high-titre antibodies to IFNβ continue to respond well to treatment and show no return of disease activity on serial MRI scans. Likewise, some patients without antibodies suffer apparent loss of treatment efficacy and a return of disease activity.

In the pivotal Phase III trial of IFNβ-1b for RRMS, 35 % of MS patients developed antibodies, and this triggered extensive study of the possible therapeutic impact of these molecules [14]. In this study, the treatment effect in patients with antibodies appeared to be less robust with respect to relapse rate, suggesting an association between the presence of antibodies and clinical response.

In this study, however, disease progression in these same patients appeared to be less marked than in those patients without antibodies. On the basis of this lack of consistent effect, the investigators concluded that decisions to discontinue IFNβ therapy should be made on a patient-by-patient basis, based on the patient's clinical response to treatment [14]. The effect of antibodies on disease progression was also analysed in a study by the European Study Group of IFNβ-1b treatment in SPMS patients. In this study, antibodies were shown not to affect disease progression as measured by EDSS score, while the effect of antibodies on relapse rates varied considerably. The data from this study therefore provide further evidence for a lack of consistent effect of antibodies on clinical outcome and that treatment decisions should be made primarily on clinical grounds [24].

A longer-term follow-up of two cohorts from the original pivotal IFNβ-1b trial has provided further data on the development of antibodies, highlighting their transient nature. This study, which followed 59 patients from Vancouver and London, Ontario, showed that in all but five patients antibodies had disappeared after 8 years of treatment. The study also showed that patients remaining antibody negative throughout the pivotal study did not subsequently develop antibodies, suggesting that they have little relevance in the longer term [27]. Subsequent analysis of data from the European Study Group in IFNβ-1b in SPMS patients also highlighted the transient nature of antibodies [24]. Approximately 50 % of antibody positive patients reverted to antibody nega-

tive at some point during the 3-year period, mirroring the results seen in the IFNβ-1b pivotal study population. Almost 80% of these patients remained antibody negative. The effect of antibody on clinical measures was also inconsistent, in line with previous studies.

The recent INCOMIN (INdependent COMparison of INterferon) study has contributed to the debate on antibodies by demonstrating that patients on high-dose IFNβ-1b (250 μg) have a better outcome with respect to clinical and MRI parameters than those receiving 30 μg IFNβ-1a, despite the increased number of IFNβ-1b-treated patients who were antibody positive [6]. Furthermore, the EVIDENCE (EVidence of Interferon Dose-response: European North American Comparative Efficacy) study, which compared once-weekly im IFNβ-1a 30 μg with thrice weekly sc IFNβ-1a 44 μg, showed that development of antibodies had no impact on time to first relapse over 48 weeks of treatment [21].

One mechanism that could explain why anti-IFNβ antibodies have so little impact on the clinical course of MS is the formation of immune complexes between IFNβ and antibody. Immune complexes can bind to Fc gamma receptors expressed by natural killer cells, B cells and monocytes, which are known to prime CD8 suppressor T cells. Therefore, both IFNβ and antigen–antibody complexes are able to activate CD8 suppressor cells, which may help suppress the activity of autoimmune cells or prevent "bystander" damage.

The FDA recently issued a memorandum stating that "there is not adequate evidence to conclude that antibodies lead to a major loss of efficacy, or that the impact of antibodies, if any, will be long lasting" [8]. The recent American Academy of Neurology Clinical Practice Treatment Guidelines concluded that several long-term, controlled randomised studies have demonstrated that although antibodies develop during IFN beta treatment, their biologic significance is, as yet, unknown and that any treatment decision must be based only on the clinical response of each individual to IFNβ [11]. I concur with these opinions.

Conclusions

The bold decision to conduct a Phase III trial of IFNβ in MS, based only on short-term results in a small number of patients, led to a major breakthrough in the treatment of this disease. IFNβ represents a key therapeutic option for MS patients as it rapidly reduces the frequency and severity of MS attacks and reduces MRI-measured disease activity. Furthermore, the progression of disability is reduced in those patients with active SPMS and the compound also improves cognition and brain metabolism.

IFNβ is well tolerated. The clinical relevance of IFNβ-related systemic side effects can be minimised by dose escalation and concomitant therapy, and injection site reactions can be largely prevented by using correct injection site rotation and an automated injector device.

Trials with IFNβ demonstrate no clear relationship between the development of antibodies and response to treatment. It is possible that immune complexes, developed when anti-interferon antibodies encounter IFNβ, might complement the effect of the drug by activating CD8 suppressor cells. Until the importance of antibodies has been elucidated, treatment decisions for patients who develop antibodies should be based on clinical response.

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The importance of maintaining effective therapy in multiple sclerosis

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Abstract The INCOMIN study (INdependent COMparison of INterferons) lends further support to the growing body of evidence that both dose and frequency of interferon beta (IFNβ) administration are important in the treatment of multiple sclerosis (MS). High-dose, high-frequency IFNβ (IFNβ-1b 250 μg eod sc and IFNβ-1a 44 μg sc) treatment offers greater therapeutic benefit, in terms of clinical and magnetic resonance imaging (MRI) outcome measures, compared with low-dose, once-weekly administration of IFNβ. The importance of maintaining the most effective treatment regimen has been shown in another study. The data from this study suggested that patients who have 'stable' disease (i. e. no evidence of clinical or MRI disease activity) during long-term treatment with IFNβ-1b 250 μg, who are subsequently treated with low-dose, once-weekly IFNβ-1a 30 μg, are more likely to experience relapses, disease progression or MRI activity compared with those remaining on IFNβ-1b 250 μg. These data clearly indicate that frequently administered therapy must

be maintained to achieve the optimal therapeutic benefit for patients. Those patients who had their IFNβ-1b 250 μg therapy reduced to low-dose, once-weekly IFNβ-1a and experienced a resumption of disease activity were returned to their previous regimen. However, after 1 year of additional follow-up, many of these patients still had clinical or MRI signs of disease activity, highlighting further the risks associated with the reduction of IFNβ dose and frequency of administration. Taking into consideration the evidence supporting the greater efficacy of IFNβ-1b 250 μg or IFNβ-1a 44 μg in MS it is of considerable interest to examine whether it is useful to increase the dose of IFNβ-1b in patients who do not respond satisfactorily to the approved standard dose. This is the rationale for the recently completed OPTIMS (OPTimization of Interferon for MS) study, in which partially responding patients were randomised to IFNβ-1b 250 or 375 μg every other day. An interim safety analysis of OPTIMS patients has not raised any safety or tolerability concerns.
In summary, there is consistent evidence to support the importance of maintaining frequently administered IFNβ (IFNβ-1b 250 μg or IFNβ-1a 44 μg) for the treatment of MS.

Key words interferon beta-1b - interferon beta-1a - multiple sclerosis - OPTIMS - INCOMIN